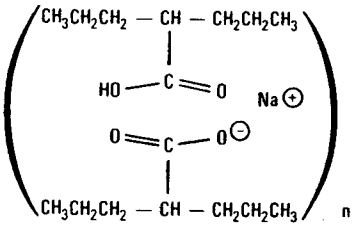
EXHIBIT 4

(Nos. 6212, 6214 and 6215)
01-2342-R5—Rev. Mar., 1985

DEPAKOTE™
DIVALPROEX SODIUM
ENTERIC-COATED TABLETS

WARNING:
HEPATIC FAILURE RESULTING IN FATALITIES HAS OCCURRED IN PATIENTS RECEIVING VALPROIC ACID AND ITS DERIVATIVES. THESE INCIDENTS USUALLY HAVE OCCURRED DURING THE FIRST SIX MONTHS OF TREATMENT. SERIOUS OR FATAL HEPATOTOXICITY MAY BE PRECEDED BY NON-SPECIFIC SYMPTOMS SUCH AS LOSS OF SEIZURE CONTROL, MALAISE, WEAKNESS, LETHARGY, FACIAL EDEMA, ANOREXIA AND VOMITING. PATIENTS SHOULD BE MONITORED CLOSELY FOR APPEARANCE OF THESE SYMPTOMS. LIVER FUNCTION TESTS SHOULD BE PERFORMED PRIOR TO THERAPY AND AT FREQUENT INTERVALS THEREAFTER, ESPECIALLY DURING THE FIRST SIX MONTHS.

DESCRIPTION
Divalproex sodium is a stable co-ordination compound comprised of sodium valproate and valproic acid in a 1:1 molar relationship and formed during the partial neutralization of valproic acid with 0.5 equivalent of sodium hydroxide. Chemically it is designated as sodium hydrogen bis(2-propylpentanoate). Divalproex sodium has the following structure:



Divalproex sodium has a molecular weight of 310.41 and occurs as a white powder with a characteristic odor.

DEPAKOTE is an oral antiepileptic supplied as enteric-coated tablets in three dosage strengths containing divalproex sodium equivalent to 125 mg, 250 mg or 500 mg of valproic acid.

CLINICAL PHARMACOLOGY
DEPAKOTE is an antiepileptic agent which is chemically related to valproic acid. It has no nitrogen or aromatic moiety characteristic of other antiepileptic drugs. The mechanism by which DEPAKOTE exerts its antiepileptic effects has not been established. It has been suggested that its activity is related to increased brain levels of gamma-aminobutyric acid (GABA). The

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effect on the neuronal membrane is unknown. DEPAKOTE dissociates into valproate in the gastrointestinal tract.

Because of the enteric coating of DEPAKOTE, absorption is delayed one hour following oral administration. Thereafter, DEPAKOTE is uniformly and reliably absorbed, as shown by studies in normal volunteers. Peak serum levels of valproate occur in 3 to 4 hours. Bioavailability of divalproex sodium tablets was found to be equivalent to that of DEPAKENE® (valproic acid) capsules. Concomitant administration with food would be expected to slow absorption but not affect the extent of absorption. The serum half-life of valproate is typically in the range of six to sixteen hours. Half-lives in the lower part of the above range are usually found in patients taking other antiepileptic drugs capable of enzyme induction.

Enteric-coated divalproex sodium may reduce the incidence of the irritative gastrointesinal effects of valproate as compared to valproic acid capsules.

Valproate is rapidly distributed and at therapeutic drug concentrations, drug is highly bound (90%) to human plasma proteins. Increases in dose may result in decreases in the extent of protein binding and increased valproate clearance and elimination.

Elimination of DEPAKOTE and its metabolites occurs principally in the urine, with minor amounts in the feces and expired air. Very little unmetabolized parent drug is excreted in the urine. The drug is primarily metabolized in the liver and is excreted as the glucuronide conjugate. Other metabolites in the urine are products of beta, omega-1, and omega oxidation (C-3, C-4 and C-5 positions). The major oxidative metabolite in the urine is 2-propyl-3-keto-pentanoic acid; minor metabolites are 2-propyl-glutaric acid, 2-propyl-5-hydroxypentanoic acid, 2-propyl-3-hydroxypentanoic acid and 2-propyl-4-hydroxypentanoic acid.

INDICATIONS AND USAGE

DEPAKOTE (divalproex sodium) is indicated for use as sole and adjunctive therapy in the treatment of simple (petit mal) and complex absence seizures. DEPAKOTE may also be used adjunctively in patients with multiple seizure types which include absence seizures.

In accordance with the International Classification of Seizures, simple absence is defined as very brief clouding of the sensorium or loss of consciousness (lasting usually 2-15 seconds), accompanied by certain generalized epileptic discharges without other detectable clinical signs. Complex absence is the term used when other signs are also present.

SEE "WARNINGS" SECTION FOR STATEMENT REGARDING FATAL HEPATIC DYSFUNCTION.

CONTRAINDICATIONS

DEPAKOTE (DIVALPROEX SODIUM) SHOULD NOT BE ADMINISTERED TO PATIENTS WITH HEPATIC DISEASE OR SIGNIFICANT DYSFUNCTION.

DEPAKOTE is contraindicated in patients with known hypersensitivity to the drug.

WARNINGS

Hepatic failure resulting in fatalities has occurred in patients receiving valproic acid. These incidents usually have occurred during the first six months of treatment. Serious or fatal hepatotoxicity may be preceded by nonspecific symptoms such as loss of seizure control, malaise, weakness, lethargy, facial edema, anorexia and vomiting. Patients should be monitored closely for appearance of these symptoms. Liver function tests should be performed prior to therapy and at frequent intervals thereafter, especially during the first six months. However, physicians should not rely totally on serum biochemistry since these tests may not be abnormal in all instances, but should also consider the results of careful interim medical history and physical examination. Caution should be observed when administering DEPAKOTE to patients with a prior history of hepatic disease. Patients on multiple anticonvulsants, children, those with congenital metabolic disorders, those with severe seizure disorders accompanied by mental retardation, and those with organic brain disease may be at particular risk.

The drug should be discontinued immediately in the presence of significant hepatic dysfunction, suspected or apparent. In some cases, hepatic dysfunction has progressed in spite of discontinuation of drug.

The frequency of adverse effects (particularly elevated liver enzymes) may be dose-related. The benefit of improved seizure control which may accompany the higher doses should therefore be weighed against the possibility of a greater incidence of adverse effects.

Usage in Pregnancy: ACCORDING TO PUBLISHED AND UNPUBLISHED REPORTS, VALPROIC ACID MAY PRODUCE TERATOGENIC EFFECTS IN THE OFFSPRING OF HUMAN FEMALES RECEIVING THE DRUG DURING PREGNANCY.

THERE ARE MULTIPLE REPORTS IN THE CLINICAL LITERATURE WHICH INDICATE THAT THE USE OF ANTIEPILEPTIC DRUGS DURING PREGNANCY RESULTS IN AN INCREASED INCIDENCE OF BIRTH DEFECTS IN THE OFFSPRING. ALTHOUGH DATA ARE MORE EXTENSIVE WITH RESPECT TO TRIMETHADIONE, PARAMETHADIONE, PHENYTOIN, AND PHENOBARBITAL, REPORTS INDICATE A POSSIBLE SIMILAR ASSOCIATION WITH THE USE OF OTHER ANTIEPILEPTIC DRUGS. THEREFORE, ANTIEPILEPTIC DRUGS SHOULD BE ADMINISTERED TO WOMEN OF CHILDBEARING POTENTIAL ONLY IF THEY ARE CLEARLY SHOWN TO BE ESSENTIAL IN THE MANAGEMENT OF THEIR SEIZURES.

THE INCIDENCE OF NEURAL TUBE DEFECTS IN THE FETUS MAY BE INCREASED IN MOTHERS RECEIVING VALPROATE DURING THE FIRST TRIMESTER OF PREGNANCY. THE CENTERS FOR DISEASE CONTROL (CDC) HAS ESTIMATED THE RISK OF VALPROIC ACID EXPOSED WOMEN HAVING CHILDREN WITH SPINA BIFIDA TO BE APPROXIMATELY 1 TO 2%. THIS RISK IS SIMILAR TO THAT FOR NONEPILEPTIC WOMEN WHO HAVE HAD CHILDREN WITH NEURAL TUBE DEFECTS (ANENCEPHALY AND SPINA BIFIDA).

ANIMAL STUDIES ALSO HAVE DEMONSTRATED VALPROIC ACID INDUCED TERATOGENICITY. Studies in rats and human females demonstrated placental transfer of the drug. Doses greater than 65 mg/kg/day given to pregnant rats and mice produced skeletal abnormalities in the offspring, primarily involving ribs and vertebrae; doses greater than 150 mg/kg/day given to pregnant rabbits produced fetal resorptions and (primarily) soft-tissue abnormalities in the offspring. In rats a dose-related delay in the onset of parturition was noted. Postnatal growth and survival of the progeny were adversely affected, particularly when drug administration spanned the entire gestation and early lactation period.

Antiepileptic drugs should not be discontinued in patients in whom the drug is administered to prevent major seizures because of the strong possibility of precipitating status epilepticus with attendant hypoxia and threat to life. In individual cases where the severity and frequency of the seizure disorder are such that the removal of medication does not pose a serious threat to the patient, discontinuation of the drug may be considered prior to and during pregnancy, although it cannot be said with any confidence that even minor seizures do not pose some hazard to the developing embryo or fetus.

The prescribing physician will wish to weigh these considerations in treating or counseling epileptic women of childbearing potential.

PRECAUTIONS

Hepatic Dysfunction: See "Contraindications" and "Warnings" sections.

General: Because of reports of thrombocytopenia, inhibition of the secondary phase of platelet aggregation, and abnormal coagulation parameters, platelet counts and coagulation tests are recommended before initiating therapy and at periodic intervals. It is recommended that patients receiving DEPAKOTE (divalproex sodium) be monitored for platelet count and coagulation parameters prior to planned surgery. Evidence of hemorrhage, bruising or a disorder of hemostasis/coagulation is an indication for reduction of

DEPAKOTE dosage or withdrawal of therapy.

Hyperammonemia with or without lethargy or coma has been reported and may be present in the absence of abnormal liver function tests. If clinically significant elevation occurs, DEPAKOTE should be discontinued.

Since DEPAKOTE (divalproex sodium) may interact with concurrently administered antiepileptic drugs, periodic serum level determinations of concomitant antiepileptic drugs are recommended during the early course of therapy. (See "Drug Interactions" section).

Valproate is partially eliminated in the urine as a keto-metabolite which may lead to a false interpretation of the urine ketone test.

There have been reports of altered thyroid function tests associated with valproate. The clinical significance of these is unknown.

Information for Patients: Since DEPAKOTE may produce CNS depression, especially when combined with another CNS depressant (e.g., alcohol), patients should be advised not to engage in hazardous occupations, such as driving an automobile or operating dangerous machinery, until it is known that they do not become drowsy from the drug.

Drug Interactions: Valproic acid may potentiate the CNS depressant activity of alcohol.

The concomitant administration of valproic acid with drugs that exhibit extensive protein binding (e.g., aspirin, carbamazepine, and dicumarol) may result in alteration of serum drug levels.

THERE IS EVIDENCE THAT VALPROIC ACID CAN CAUSE AN INCREASE IN SERUM PHENOBARBITAL LEVELS BY IMPAIRMENT OF NONRENAL CLEARANCE. THIS PHENOMENON CAN RESULT IN SEVERE CNS DEPRESSION. THE COMBINATION OF VALPROIC ACID AND PHENOBARBITAL HAS ALSO BEEN REPORTED TO PRODUCE CNS DEPRESSION WITHOUT SIGNIFICANT ELEVATIONS OF BARBITURATE OR VALPROATE SERUM LEVELS. ALL PATIENTS RECEIVING CONCOMITANT BARBITURATE THERAPY SHOULD BE CLOSELY MONITORED FOR NEUROLOGICAL TOXICITY. SERUM BARBITURATE LEVELS SHOULD BE OBTAINED, IF POSSIBLE, AND THE BARBITURATE DOSAGE DECREASED, IF APPROPRIATE.

Primidone is metabolized into a barbiturate and, therefore, may also be involved in a similar or identical interaction.

THERE HAVE BEEN REPORTS OF BREAKTHROUGH SEIZURES OCCURRING WITH THE COMBINATION OF VALPROIC ACID AND PHENYTOIN. MOST REPORTS HAVE NOTED A DECREASE IN TOTAL PLASMA PHENYTOIN CONCENTRATION. HOWEVER, INCREASES IN TOTAL PHENYTOIN SERUM CONCENTRATION HAVE BEEN REPORTED. AN INITIAL FALL IN TOTAL PHENYTOIN LEVELS WITH SUBSEQUENT INCREASE IN PHENYTOIN LEVELS HAS ALSO BEEN REPORTED. IN ADDITION, A DECREASE IN TOTAL SERUM PHENYTOIN WITH AN INCREASE IN THE FREE VS. PROTEIN BOUND PHENYTOIN LEVELS HAS BEEN REPORTED. THE DOSAGE OF PHENYTOIN SHOULD BE ADJUSTED AS REQUIRED BY THE CLINICAL SITUATION.

THE CONCOMITANT USE OF VALPROIC ACID AND CLONAZEPAM MAY PRODUCE ABSENCE STATUS.

There is inconclusive evidence regarding the effect of valproate on serum ethosuximide levels. Patients receiving valproate and ethosuximide, especially along with other anticonvulsants, should be monitored for alterations in serum concentrations of both drugs.

Caution is recommended when DEPAKOTE (divalproex sodium) is administered with drugs affecting coagulation, e.g., aspirin and warfarin. (See "Adverse Reactions" section).

Carcinogenesis: Valproic acid was administered to Sprague Dawley rats and ICR (HA/ICR) mice at doses of 0, 80 and 170 mg/kg/day for two years. Although a variety of neoplasms were observed in both species, the chief findings were a statistically significant increase in the incidence of subcutaneous fibrosarcomas in high dose male rats receiving valproic acid and a statistically significant dose-related trend for benign pulmonary adenomas in male mice receiving valproic acid. The sig-

nificance of these findings for man is unknown at present.

Mutagenesis: Studies on valproic acid have been performed using bacterial and mammalian systems. These studies have provided no evidence of a mutagenic potential for DEPAKOTE.

Fertility: Chronic toxicity studies in juvenile and adult rats and dogs demonstrated reduced spermatogenesis and testicular atrophy at doses greater than 200 mg/kg/day in rats and greater than 90 mg/kg/day in dogs. Segment I fertility studies in rats have shown doses up to 350 mg/kg/day for 60 days to have no effect on fertility. THE EFFECT OF DEPAKOTE (DIVALPROEX SODIUM) ON THE DEVELOPMENT OF THE TESTES AND ON SPERM PRODUCTION AND FERTILITY IN HUMANS IS UNKNOWN.

Pregnancy: Pregnancy Category D: See "Warnings" section.

Nursing Mothers: Valproate is excreted in breast milk. Concentrations in breast milk have been reported to be 1-10% of serum concentrations. It is not known what effect this would have on a nursing infant. Caution should be exercised when DEPAKOTE is administered to a nursing woman.

ADVERSE REACTIONS

Since valproic acid and its derivatives have usually been used with other antiepileptic drugs, it is not possible, in most cases, to determine whether the following adverse reactions can be ascribed to valproic acid alone, or the combination of drugs.

Gastrointestinal: The most commonly reported side effects at the initiation of therapy are nausea, vomiting and indigestion. These effects are usually transient and rarely require discontinuation of therapy. Diarrhea, abdominal cramps and constipation have been reported. Both anorexia with some weight loss and increased appetite with weight gain have also been reported. The administration of enteric-coated divalproex sodium may result in reduction of gastrointestinal side effects in some patients.[2]

CNS Effects: Sedative effects have been noted in patients receiving valproic acid alone but are found most often in patients receiving combination therapy. Sedation usually disappears upon reduction of other antiepileptic medication. Tremor has been reported in patients receiving valproate and may be dose-related. Ataxia, headache, nystagmus, diplopia, asterixis, "spots before eyes," dysarthria, dizziness, and incoordination have rarely been noted. Rare cases of coma have been noted in patients receiving valproic acid alone or in conjunction with phenobarbital.

Dermatologic: Transient increases in hair loss have been observed. Skin rash and erythema multiforme rarely have been noted.

Psychiatric: Emotional upset, depression, psychosis, aggression, hyperactivity and behavioral deterioration have been reported.

Musculoskeletal: Weakness has been reported.

Hematologic: Thrombocytopenia has been reported. Valproic acid inhibits the secondary phase of platelet aggregation. (See "Drug Interactions" section). This may be reflected in altered bleeding time. Petechiae, bruising, hematoma formation, and frank hemorrhage have been reported. (See "Precautions" section). Relative lymphocytosis and hypofibrinogenemia have been noted. Leukopenia and eosinophilia have also been reported. Anemia and bone marrow suppression have been reported.

Hepatic: Minor elevations of transaminases (e.g., SGOT and SGPT) and LDH are frequent and appear to be dose related. Occasionally, laboratory test results include, as well, increases in serum bilirubin and abnormal changes in other liver function tests. These results may reflect potentially serious hepatotoxicity. (See "Warnings" section).

Endocrine: There have been reports of irregular menses and secondary amenorrhea, and rare reports of breast enlargement and galactorrhea occurring in patients receiving valproic acid and its derivatives.

Abnormal thyroid function tests have been reported. (See "Precautions" section).

Pancreatic: There have been reports of acute pancreatitis, including rare fatal cases, occurring in patients receiving valproic acid and its derivatives.

Metabolic: Hyperammonemia. (See "Precautions" section).

Hyperglycinemia has been reported and has been associated with a fatal outcome in a patient with preexistent nonketotic hyperglycinemia.

Other: Edema of the extremities has been reported.

OVERDOSAGE

Overdosage with valproic acid may result in deep coma.

Since DEPAKOTE tablets are enteric-coated, the benefit of gastric lavage or emesis will vary with the time since ingestion. General supportive measures should be applied with particular attention being given to the maintenance of adequate urinary output.

Naloxone has been reported to reverse the CNS depressant effects of valproate overdosage. Because naloxone could theoretically also reverse the antiepileptic effects of DEPAKOTE it should be used with caution.

DOSAGE AND ADMINISTRATION

DEPAKOTE is administered orally. The recommended initial dose is 15 mg/kg/day, increasing at one week intervals by 5 to 10 mg/kg/day until seizures are controlled or side effects preclude further increases. The maximum recommended dosage is 60 mg/kg/day. If the total daily dose exceeds 250 mg, it should be given in a divided regimen.

Conversion from DEPAKENE to DEPAKOTE: In patients previously receiving DEPAKENE (valproic acid) therapy, DEPAKOTE should be initiated at the same total daily dose and dosing schedule.[3] After the patient is stabilized on DEPAKOTE, a twice-a-day or three-times-a-day schedule may be instituted in selected patients.

The frequency of adverse effects (particularly elevated liver enzymes) may be dose-related. The benefit of improved seizure control which may accompany higher doses should therefore be weighed against the possibility of a greater incidence of adverse reactions.

A good correlation has not been established between daily dose, serum level and therapeutic effect. However, therapeutic valproate serum levels for most patients will range from 50 to 100 mcg/ml. Occasional patients may be controlled with serum levels lower or higher than this range.

As the DEPAKOTE dosage is titrated upward, blood levels of phenobarbital and/or phenytoin may be affected. (See "Precautions" section).

Patients who experience G. I. irritation may benefit from administration of the drug with food or by slowly building up the dose from an initial low level.

HOW SUPPLIED

DEPAKOTE (divalproex sodium enteric-coated tablets) are supplied as:

125 mg salmon pink-colored tablets:
Bottles of 100 ..... (NDC 0074-6212-13)

250 mg peach-colored tablets:
Bottles of 100 ..... (NDC 0074-6214-13)
Abbo-Pac® unit dose packages of
100 ..... (NDC 0074-6214-11).

500 mg lavender-colored tablets:
Bottles of 100 ..... (NDC 0074-6215-13)
Abbo-Pac® unit dose packages of
100 ..... (NDC 0074-6215-11).

REFERENCES

1. Centers for Disease Control, Valproate: A New Cause of Birth Defects — Report from Italy and Follow-up from France, *Morbidity and Mortality Weekly Report* 32(33):438-439, August 26, 1983.
2. Wilder, B.J., et al, Gastrointestinal Tolerance of Divalproex Sodium, *Neurology* 33:808-811, June, 1983.
3. Wilder, B.J., et al, Twice-Daily Dosing of Valproate with Divalproex, *Clin Pharmacol Ther* 34(4): 501-504, 1983.

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